



Activation of lymphangiogenesis by platelet as novel therapeutic approaches for liver cirrhosis and portal hypertension

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Abstract

This letter comments on the recently published article in the *World Journal of Gastroenterology*, in which the authors demonstrated a strong link between lymphangiogenesis and the process of platelet adherence, aggregation, and activation by employing a rat model of liver cirrhosis caused by bile duct ligation (BDL). The authors applied both gain and loss of function approach by using platelet-rich plasma and vascular endothelial growth factor 3 receptor inhibitor MAZ-51 to activate and inhibit angiogenetic signaling in BDL rat model, respectively, to verify the crucial function of lymphangiogenesis in the development of liver cirrhosis and portal hypertension (PHT). In clinical practice, platelet transfusion has been applied to improve liver function in patients suffering from chronic liver disease and cirrhosis. Therefore, this study provides support for the application of platelet transfusion or pharmacological intervention of lymphangiogenesis as novel therapeutic approaches for liver cirrhosis and PHT.

Key Words: Portal hypertension; Liver cirrhosis; Lymphangiogenesis; Platelets; Vascular endothelial growth factor C

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Core Tip: Whole-transcriptome sequencing in rat model of liver cirrhosis induced by bile duct ligation revealed the strong link between lymphangiogenesis and the process of platelet adherence, aggregation, and activation. Gain and loss of function approach confirmed the crucial function of lymphangiogenesis in the development of liver cirrhosis and portal hypertension (PHT). In conclusion, this study provides support for the application of platelet transfusion or pharmacological intervention of lymphangiogenesis as novel therapeutic approaches for liver cirrhosis and PHT.

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TO THE EDITOR

Lymphangiogenesis is the process of creating new lymphatic vessels from existing ones and is a crucial aspect of wound healing[1,2]. Upon injury, new lymphatic vessel will form to transport immune cells, proteins, and fluid out of the injured region. An early study has revealed the association between blood clotting and lymphangiogenesis during wound healing and demonstrated that platelets mechanistically promote lymphangiogenesis by secreting vascular endothelial growth factor C (VEGF-C) and activating the VEGF-C/VEGF receptor 3 (VEGFR-3) pathway in lymphatic endothelial cells[3].

It is known that liver cirrhosis and portal hypertension (PHT) can cause lymphatic abnormalities because of increased resistance in the liver's blood vessels and elevated blood flow in the portal vein[4,5]. In the course of liver fibrosis, lymphatic system experiences a series of structural and functional alterations to alleviate local inflammation and hepatic circulatory pressure[6]. Indeed, boosting the quantity of lymphatic vessels in the course of liver fibrosis and cirrhosis could prevent fiber accumulation[7]. Therefore, how to promote lymphangiogenesis in the liver may be a novel approach to the treatment of liver cirrhosis and PHT, which are high risk factors of hepatocellular carcinoma[8-11].

In this context, a recent study employed whole-transcriptome sequencing to identify changes in lymphatic system in rat model of liver cirrhosis caused by bile duct ligation (BDL)[12]. Notably, the authors found the enrichment of platelets-related pathways, suggesting their association with lymphangiogenesis in liver cirrhosis and PHT. These results are consistent with previous findings that platelets have the capability to induce lymphangiogenesis and alleviate liver cirrhosis[13,14]. While Chen *et al*[12] established the platelet-lymphangiogenesis connection in experimental cirrhosis, this commentary identifies immediate clinical opportunities to translate these findings through platelet-based therapies.

MAIN FINDINGS OF THIS STUDY

First, the authors employed whole-transcriptome sequencing to identify changes in lymphatic system in BDL rat model, and found that lymphatic vessels increased and lymphangiogenesis related genes, especially VEGF-C, were upregulated in BDL rat model. Next, the authors applied VEGF-C to augment the lymphatic system in rat model, and found less liver fibrosis. Furthermore, molecular profiling of the differentially expressed genes in BDL model rats compared to sham-operated control rats showed that the leading 30 enriched biological processes involved the enhancement of platelet activation and inflammatory response. Gene Ontology analysis revealed an enrichment in wound healing, platelet alpha granules, platelet alpha granule lumen, platelet alpha granule membrane, and platelet dense granules. As expected, the application of VEGFR inhibitor MAZ-51 significantly decreased the quantity of lymphatic vessels and downregulated the expression of platelet markers. However, the application of platelet-rich plasma (PRP) in BDL rat model improved liver cirrhosis and PHT by inhibiting intrahepatic angiogenesis and alleviating inflammatory response.

THE LIMITATIONS OF THIS STUDY

This study has several limitations. First, the findings are based solely on BDL rat model, which may not accurately mimic the pathogenesis of liver fibrosis and cirrhosis in human body. Therefore, further studies using other models and human samples will be necessary to confirm the role of lymphangiogenesis in liver cirrhosis and PHT and the application of platelet for the therapy of liver cirrhosis and PHT[15]. Second, a variety of cells participate in the regulation of lymphangiogenesis in the liver. The authors only examined lymphatic endothelial cells. Further studies are needed to investigate the role of other cells such as hepatic stellate cells[16]. Third, angiogenesis is a ubiquitous process involving all organs

and tissues in the body. Therefore, we should consider side effects and safety issue for the drugs targeting angiogenesis signal pathway[17]. In addition, genetic variants will affect the response of the individual to the drugs targeting angiogenesis signal pathway[18,19]. In future clinical investigations, we should compare the effects of platelets on liver lymphangiogenesis in individuals with different genetic background.

CLINICAL SIGNIFICANCE OF THIS STUDY

Despite the above limitations, this study has significant clinical significance. First, the authors employed molecular profiling to reveal the close association between lymphangiogenesis and platelet adherence, aggregation and activation in the liver. Second, the authors applied both gain and loss of function approach by using PRP and MAZ-51 to activate and inhibit angiogenic signaling in BDL rat model, respectively, to confirm the crucial function of lymphangiogenesis in the development of liver cirrhosis and PHT. Indeed, PRP has shown promise in ameliorating liver injury induced by carbon tetrachloride and thioacetamide and improving liver fibrosis[20-22]. Interestingly, molecular profiling of the differentially expressed genes in patients with hypertrophic cardiomyopathy showed that platelet activation signaling was also associated with hypertrophic cardiomyopathy, indicating that platelet activation may also promote lymphangiogenesis in other diseased conditions[23].

THERAPEUTIC OPPORTUNITIES BEYOND THE ORIGINAL STUDY

A recent study showed that PRP derived extracellular vesicles improved liver cirrhosis in mouse model[24]. In clinical practice, platelet transfusion has been applied to improve liver function in patients suffering from chronic liver disease and cirrhosis[25]. In addition, antiangiogenic drug regorafenib could alleviate PHT by inhibiting liver fibrosis[26]. While VEGF-C/VEGFR-3 axis is the primary driver of lymphangiogenesis, recent evidence indicates that other factors and pathways also regulate lymphangiogenesis, offering additional targets for therapeutic intervention[27]. All these results suggest promising potential of platelet transfusion or pharmacological intervention of lymphangiogenesis as novel therapeutic approaches for liver cirrhosis and PHT.

CONCLUSION

Up to now, there are still some gaps in our knowledge of how platelet transfusion improves liver function in patients suffering from chronic liver disease and cirrhosis. Further understanding of the underlying mechanisms will provide new directions for clinical translation of platelet transfusion. In addition, clinical trials to evaluate the safety of PRP for liver cirrhosis, the standardization of PRP preparation protocols, and the monitoring of portal thrombosis risk will validate the application of RRP in the clinic.

FOOTNOTES

Author contributions: Li JF and Wang QB contributed equally as co-first authors; Li JF, Wang QB, Li YK, Liang YB, and Chen XM interpreted the data and drafted the manuscript; Lu QY and Ke Y designed the letter and reviewed and edited it critically; all authors approved the final version to be published and agreed to be accountable for all aspects of the manuscript.

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